PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Shiv Kumar AGARWAL et al. Group Art Unit: 1614

Application No.: 10/827,368

Filed: April 20, 2004 Docket No.: 115683.01

For: NOVEL PYRIMIDON DERIVATIVES

CLAIM FOR PRIORITY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The benefit of the filing date of the following prior foreign application filed in the following foreign country is hereby requested for the above-identified patent application and the priority provided in 35 U.S.C. §119 is hereby claimed:

Indian Patent Application No. 266/MAS/2002 filed on October 4, 2002

In support of this claim, a certified copy of said original foreign application:

☒ is filed herewith.

It is requested that the file of this application be marked to indicate that the requirements of 35 U.S.C. §119 have been fulfilled and that the Patent and Trademark Office kindly acknowledge receipt of this document.

Respectfully submitted,

James A. Oliff
Registration No. 27,075

Joel S. Armstrong
Registration No. 36,430

JAO:JSA/mlo

Date: August 30, 2004

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Alexandria, Virginia 22320
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DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry;
Charge any fee due to our Deposit Account No. 15-0461

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Provisional Specification & Abstract of the extract of Patent Application No.266/MAS/2002, dated 10/04/2002 by M/s. Orchid Chemicals & Pharmaceuticals Limited, having its registered office at 1, 6th Floor, Crown Court, 34, Cathedral Road, Chennai 600 086, Tamil Nadu, India.

.....

.....In witness thereof

I have hereunto set my hand

Dated this the 19th day of July 2004

M.S. Venkataraman

(M.S. VENKATARAMAN)
Assistant Controller of Patents & Designs

ATE OFFICE BRANCH
OVE MENT OF INDIA
una mplex, 6th Floor, Annex.II
o.443 nna Salai, Teynampet,Chennai – 600 018

FORM 1
THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Orchid Chemicals& Pharmaceuticals Ltd., an Indian company having its registered office at 1,6th Floor, Crown Court, 34, Cathedral Road, TN, Chennai - 600 086, India hereby declare

1.(a) that we are in possession of an invention titled **NEW PYRIMIDONE DERIVATIVES AS CYCLOOXYGENASE-2 INHIBITORS**

(b) that the provisional specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are

1. Shiv Kumar Agarwal,
1A, Smrithi,
No. 4, Beach Road
Kalakshetra Colony
Besant Nagar,
Chennai 600 090.

2. Tadiparthi Ravikumar,
F-3, Jayashree Flats,
Opp.Perungudi panchayat office,
Perungudi,
Chennai – 600 096.

3. Pawan Aggarwal,
H-98/ S-2, T.N.H.B Flats,
First Seaward Road,
Valmiki Nagar,
Thiruvanmiyur,
Chennai - 600 041.

3. that we are the assignee of the true and first inventors

4. that our address for service in India is as follows;

Dr. C. B. Rao
Orchid Chemicals& Pharmaceuticals Ltd.,
1,6th Floor, Crown Court,
34, Cathedral Road, TN, Chennai - 600 086, India

5. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) _____
Shiv Kumar Agarwal

(Signed) _____
Tadiparthi Ravikumar

(Signed) _____
Pawan Aggarwal

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
(a) complete specification (23 pages, in triplicate)
(b) abstract of the invention (1 page, in triplicate)
(c) fee Rs. 5000.00 (five thousand rupees only) in bankers cheque bearing No.120219 dated April 9, 2002, drawn on ICICI bank, Chennai.

We request that a patent may be granted to us for the said invention

Dated this tenth (10th) day of April 2002

(Signed) _____
Dr. C. B. Rao
Dy. Managing Director
Orchid Chemicals& Pharmaceuticals Ltd

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

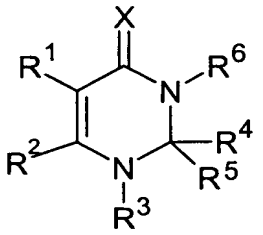
NEW PYRIMIDONE DERIVATIVES AS CYCLOOXYGENASE-2 INHIBITORS

Orchid Chemicals & Pharmaceuticals Ltd.
An Indian Company having its registered office at
1,6th Floor, Crown Court,
34, Cathedral Road
Chennai - 600 086, India

The following specification describes the nature of this invention

Field of the Invention

The present invention provides novel compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them. The present invention more particularly provides novel pyrimidone derivatives of the general formula (I).



(I)

The present invention also provides a process for the preparation of the above said novel pyrimidone derivatives of the formula (I) their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.

The novel pyrimidone derivatives of the present invention may be useful in the treatment of conditions such as inflammation, arthritis, pain, fever, psoriasis, allergic diseases, asthma, inflammatory bowel syndrome, gastro-intestinal ulcers, cardiovascular disorders including ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, particularly brain damage caused by stroke, other inflammatory conditions and disorders associated with free radicals. The compounds of the present invention may also be useful in the treatment of conditions such as acne, sunburn, eczema and in the treatment of leukotriene-mediated pulmonary, gastrointestinal, dermatological and cardiovascular inflammatory conditions. Different types of

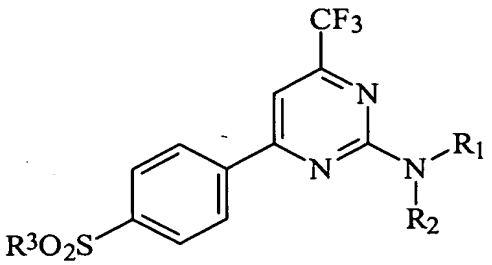
arthritis such as rheumatoid arthritis, osteoarthritis can also be treated using compounds of formula (I). Conditions such as inflammation, gastric disorders enumerated can be treated by inhibiting lipoxygenase and cyclooxygenase (COX) enzymes. Specifically the compounds of the present invention are selective COX-2 inhibitors.

Background of Invention

It has been reported that Cyclooxygenase enzymes exist in two forms, namely, COX-1 and COX-2. COX-1 enzyme is essential and primarily responsible for the regulation of gastric fluids whereas COX-2 enzyme is present at the basal levels and is reported to have a major role in the prostaglandin synthesis for inflammatory response. These prostaglandins are known to cause inflammation in the body. Hence, if the synthesis of these prostaglandins is stopped by way of inhibiting COX-2 enzyme, inflammation and its related disorders can be treated. Recent reports show that inhibitors of COX-1 enzyme causes gastric ulcers, where as selective COX-2 enzyme inhibitors are devoid of this function and hence are found to be safe.

Few pyrimidine based COX-2 inhibitors have been reported in the literature, which are as given here:

International Patent publication WO 01/3811 discloses compounds of the formula



(II)

in which: R^1 and R^2 are independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{3-10} cycloalkyl, C_{0-6} alkyl or C_{4-12} bridged cycloalkane; and R^3 is C_{1-6} alkyl or NH_2. Compounds of formula (I) are potent and selective inhibitors of COX-2 and are of use in the treatment of the pain, fever, inflammation of a variety of conditions and diseases.

United States patent 5,284,949 discloses 2-substituted amino-4,6-di-tertiarybutyl-5-hydroxy-1,3-pyrimidines and their pharmaceutically acceptable acid addition or base addition salts, pharmaceutical compositions and methods of use. The invention compounds are described as inhibitors of 5-lipoxygenase and /or cyclooxygenase providing treatment of conditions advantageously affected by such inhibition including inflammation, arthritis, pain, fever and the like.

United States patents 5,340,815 and 5302597 disclose 2-substituted-4,6-di-tertiarybutyl-5-hydroxy-1,3-pyrimidines and pharmaceutically acceptable acid addition or base addition salts thereof, pharmaceutical compositions and methods of use therefor. These compounds are claimed as inhibitors of 5-lipoxygenase and /or cyclooxygenase.

United States patent 5,356,898 discloses 4,6-di-tertiarybutyl-5-hydroxy-1,3-pyrimidines substituted 1,2,4- and 1,3,4-thiadiazoles and oxadiazoles and 1,2,4-triazoles, and pharmaceutically acceptable acid addition and base addition salts thereof, pharmaceutical compositions and methods of use therefor. The invention compounds are claimed to have 5-lipoxygenase and / or cyclooxygenase inhibiting activity. Thereby useful in the treatment of inflammation, arthritis, pain, fever and particularly rheumatoid arthritis, osteoarthritis, other inflammatory conditions, psoriasis, allergic diseases, asthma, inflammatory bowel disease, GI ulcers, cardiovascular conditions, including ischemic heart disease and atherosclerosis, and ischemia-induced cell damage, particularly brain damage caused by stroke mediated by these

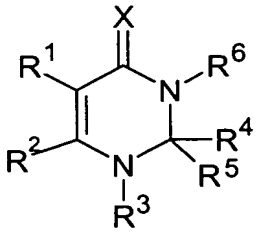
enzymes. They can also be used topically for treating acne, sunburn, psoriasis and eczema. The disclosed compounds also have potential utility as antioxidants and preferably in treating inflammatory conditions.

Objective of the Invention

We have focussed our research to identify selective COX-2 inhibitors which are devoid of any side effects normally associated with anti-inflammatory agents. Our sustained efforts have resulted in novel pyrimidone derivatives of the formula (I). The derivatives may be useful in the treatment of inflammation, arthritis, pain, fever, psoriasis, allergic diseases, asthma, inflammatory bowel syndrome, gastrointestinal ulcers, cardiovascular disorders including ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, particularly brain damage caused by stroke, and other inflammatory conditions and disorders associated with free radicals.

Summary of the Invention

The present invention relates to novel pyrimidone derivatives of the formula (I)



(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, wherein X represents oxygen or sulfur; R^1 and R^2 may be same or different and independently represent hydrogen, halogen, hydroxyl, nitro, cyano, azido,

nitroso, amino, formyl or unsubstituted or substituted groups selected from alkyl, aryl, cycloalkyl, acyl, alkoxy, aryloxy, heterocyclyl, heteroaryl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives; R^3 and R^6 may be same or different and independently represent hydroxyl, formyl or unsubstituted or substituted groups selected from alkyl, aryl, cycloalkyl, acyl, heterocyclyl, heteroaryl, monoalkylamino, dialkylamino, acylamino or alkoxyalkyl groups; R^4 represents $-Z-R^7$, where Z represents a bond, C(=O), CH_2 or NH, R^7 represents hydrogen, hydroxyl, formyl or unsubstituted or substituted groups selected from alkyl, aryl, cycloalkyl, heterocyclyl, acyl, heteroaryl or alkoxyalkyl groups; R^5 represents hydrogen or together with R^4 represent =Y, where Y represents oxygen or sulfur; R^3 and R^5 may together also form a double bond.

Detailed Description of the Invention

Suitable groups represented by R^1 and R^2 may be selected from hydrogen, halogen atom such as fluorine, chlorine, bromine, iodine; hydroxyl, nitro, cyano, azido, nitroso, amino, formyl or unsubstituted or substituted, linear or branched (C_1-C_6) alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; aryl group such as phenyl or naphthyl, the aryl group may be substituted; cyclo (C_3-C_6) alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; acyl group such as $-C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl and the like, which may be substituted; unsubstituted or substituted, linear or branched (C_1-C_6) alkoxy group, such as methoxy, ethoxy, n-propoxy, isopropoxy and the like; aryloxy

group such as phenoxy, napthoxy, the aryloxy group may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like, the heterocyclyl group may be substituted; heteroaryl group may be mono or fused system such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrolyl, benzoxadiazolyl, benzothiadiazolyl and the like, the heteroaryl group may be substituted; monoalkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, and the like, which may be substituted; dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like, which may be substituted; acylamino group such as $NHC(=O)CH_3$, $NHC(=O)C_2H_5$, $NHC(=O)C_3H_7$, $NHC(=O)C_6H_{13}$, and the like, which may be substituted; alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl and the like, the alkoxycarbonyl group may be substituted; aryloxycarbonyl group such as phenoxycarbonyl, napthoxycarbonyl, the aryloxycarbonyl group may be substituted; alkylsulfonyl group such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, iso-propylsulfonyl and the like, the alkylsulfonyl group may be substituted; arylsulfonyl group such as phenylsulfonyl or naphthylsulfonyl, the arylsulfonyl group may be substituted; alkylsulfinyl group such as methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, iso-propylsulfinyl and the like, the alkylsulfinyl group may be substituted; arylsulfinyl group such as phenylsulfinyl or naphthylsulfinyl, the arylsulfinyl group may be substituted; alkylthio group such as methylthio, ethylthio, n-propylthio, iso-propylthio and the like, the alkylthio group may be substituted; arylthio group such as phenylthio, or naphthylthio, the arylthio group may be substituted; alkoxyalkyl group such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and

the like, which may be substituted; carboxylic acid or its derivatives such as esters, amides and acid halides.

Suitable groups represented by R^3 and R^6 may be selected from hydroxyl, formyl or unsubstituted or substituted, linear or branched (C_1-C_6) alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, hexyl and the like; aryl group such as phenyl or naphthyl, the aryl group may be substituted; cyclo (C_3-C_6) alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; acyl group such as $-C(=O)CH_3$, $-C(=O)C_2H_5$, $-C(=O)C_3H_7$, $-C(=O)C_6H_{13}$, $-C(=S)CH_3$, $-C(=S)C_2H_5$, $-C(=S)C_3H_7$, $-C(=S)C_6H_{13}$, benzoyl and the like, which may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like, the heterocyclyl group may be substituted; heteroaryl group may be mono or fused system such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrolyl, benzoxadiazolyl, benzothiadiazolyl and the like, the heteroaryl group may be substituted; monoalkylamino group such as $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_6H_{13}, and the like, which may be substituted; dialkylamino group such as $N(CH_3)_2$, $NCH_3(C_2H_5)$, $N(C_2H_5)_2$ and the like, which may be substituted; acylamino group such as $NHC(=O)CH_3$, $NHC(=O)C_2H_5$, $NHC(=O)C_3H_7$, $NHC(=O)C_6H_{13}$, and the like, which may be substituted; alkoxyalkyl groups such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted.

Suitable groups represented by R^7 may be selected from hydrogen, hydroxyl, formyl or unsubstituted or substituted, linear or branched (C_1-C_6) alkyl group, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-

butyl, n-pentyl, isopentyl, hexyl and the like; aryl group such as phenyl or naphthyl, the aryl group may be substituted; cyclo (C_3-C_6) alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, the cycloalkyl group may be substituted; acyl group such as -C(=O)CH_3, -C(=O)C_2H_5, -C(=O)C_3H_7, -C(=O)C_6H_{13}, -C(=S)CH_3, -C(=S)C_2H_5, -C(=S)C_3H_7, -C(=S)C_6H_{13}, benzoyl and the like, which may be substituted; heterocyclyl groups such as aziridinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, and the like, the heterocyclyl group may be substituted; heteroaryl group may be mono or fused system such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyrimidinyl, benzopyranyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzopyrolyl, benzoxadiazolyl, benzothiadiazolyl and the like, the heteroaryl group may be substituted; groups such as methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like, which may be substituted.

The substituents on the groups R^1, R^2, R^3, R^4, R^6, R^7 may be selected from halogen, hydroxy, nitro, cyano, azido, nitroso, amino, formyl, alkyl, aryl, cycloalkyl, alkoxy, aryloxy, heterocyclyl, heteroaryl, monoalkylamino, dialkylamino, acylamino, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl, alkoxyalkyl groups or carboxylic acids or its derivatives and these substituents are as defined above.

Pharmaceutically acceptable salts of the present invention include salts of the carboxylic acid moiety such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as diethanolamine, α-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Salts also include amino acid salts such

as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, guanidine etc. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, tosylates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

Representative compounds according to the present invention include:

4-Methanesulfonyl-6-oxo-1-(4-sulfamoyl-phenyl)-2-(4-trifluoromethyl-phenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid ethyl ester;
4-Methanesulfonyl-1-(4-methanesulfonyl-phenyl)-6-oxo-2-(4-trifluoromethyl-phenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid ethyl ester;
4-Methanesulfonyl-2-(4-sulfamoyl-phenyl)-6-oxo-1-(4-trifluoromethyl-phenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid ethyl ester;
4-Methanesulfonyl-2-(4-methanesulfonyl-phenyl)-6-oxo-1-(4-trifluoromethyl-phenyl)-1,6-dihydro-pyrimidine-5-carboxylic acid ethyl ester;
4-[1,3-Dimethyl-2,4-dioxo-6-(4-trifluoromethyl-phenyl)-1,2,3,4-tetrahydro-pyrimidin-5-yl]-benzenesulfonamide;
5-(4-Methanesulfonyl-phenyl)-1,3-dimethyl-6-(4-trifluoromethyl-phenyl)-1H-pyrimidine-2,4-dione;
4-[1,3-Dimethyl-2,6-dioxo-5-(4-trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyrimidin-4-yl]-benzenesulfonamide;
6-(4-Methanesulfonyl-phenyl)-1,3-dimethyl-5-(4-trifluoromethyl-phenyl)-1H-pyrimidine-2,4-dione;
4-[5-Cyano-1-methyl-2,6-dioxo-3-(4-trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyrimidin-4-yl]-benzenesulfonamide;
6-(4-methanesulfonyl-phenyl)-3-methyl-2,4-dioxo-1-(4-trifluoromethyl-phenyl)-1,2,3,4-tetrahydropyrimdin-5-carbonitrile;

4-[5-Cyano-3-methyl-2,4-dioxo-6-(4-trifluoromethyl-phenyl)-3,4-dihydro-2H-pyrimidine-1-yl]-benzensulfonamide;

1-(4-Methanesulfonyl-phenyl)-3-methyl-2,4-dioxo-6-(4-trifluoromethyl-phenyl)-1,2,3,4-tetrahdyropyrimidine-5-carbonitrile;

4-Oxo-6-(4-sulfamoyl-phenyl)-2-thioxo-1-p-tolyl-3-trifluoromethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylicacid ethyl ester;

6-(4-Methanesulfonyl-phenyl)-4-oxo-2-thioxo-1-p-tolyl-3-trifluoromethyl-1,2,3,4-tetrahydropyrimidine-5-carboxylicacid ethyl ester;

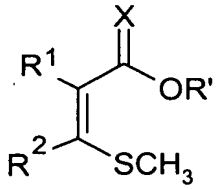
4-Cyano-6-oxo-2-(4-sulfamoyl-phenylamino)-1-(4-trifluoromethyl-phenyl)-1,6-dihydropyrimidine-5-carboxylic acid ethyl ester;

4-Cyano-2-(4-methanesulfonyl-phenylamino)-6-oxo-1-(4-trifluormethyl-phenyl)-1,6-dihydropyrimidine-5-carboxylic acid ethyl ester;

4-[5-Cyano-4-methanesulfonyl-6-oxo-1-(4-trifluoromethyl-phenyl)-1,6-dihydro-pyrimidin-2yl-amino]benzenesulfonamide;

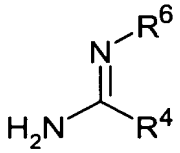
4-[5-Cyano-6-methanesulfonyl–4-oxo-2-(4-methanesulfonyl-phenylamino)-1-(4-trifluoromethyl-phenyl)-1,4-dihydropyrimidine-2-yl-amino] benzenesulfonamide;

According to another embodiment of the present invention, there is provided a process for the preparation of novel pyrimidone derivatives of the formula (I) where R^4 represent $-Z-R^7$, Z represents a bond and R^6 and R^7 represent unsubstituted or substituted aryl group wherein either R^6 and R^7 are substituted with atleast one of the groups selected from alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl, which comprises reacting a compound of the formula (Ia)



(Ia)

where R' represent (C_1-C_3) alkyl group and all other symbols are as defined earlier, with a compound of the formula (Ib)

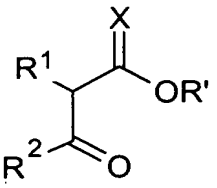


(Ib)

where R^4, R^6 are as defined earlier to produce a compound of formula (I).

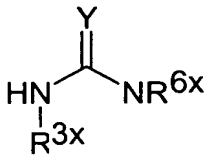
The reaction of compound of formula (Ia) with compound of formula (Ib) may be carried out using appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethylacetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalchol, acetic acid, propionic acid etc, a mixture thereof or the like. The condensation reaction is carried out by using acidic condition: mineral or organic acids, or basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals. The reaction is carried out by using phase transfer catalysts viz. triethylbenzylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium hydrogensulphate, tricaprylylmethylammonium chloride (aliquat 336) and the like. The reaction is usually carried out under cooling to refluxing conditions. The final product purified by using chromatographic techniques or by recrystallization.

According to yet another embodiment of the present invention, there is provided a process for the preparation of novel pyrimidone derivatives of the formula (I) where R^1 and R^2 represent unsubstituted or substituted aryl group wherein either R^1 and R^2 are substituted with atleast one of the groups selected from alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl and all other symbols are as defined earlier which comprises reacting a compound of the formula (Ic)



(Ic)

where R' represent (C_1-C_3) alkyl group and all other symbols are as defined earlier, with a compound of the formula (Id)



(Id)

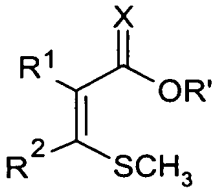
where R^{3x} represents hydrogen and all other symbols defined for R^3, R^{6x} represents hydrogen and all other symbols defined for R^6 defined earlier, Y represents oxygen or sulfur to produce a compound of formula (I) defined above.

The reaction of compound of formula (Ic) with compound of formula (Id) may be carried out using appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, acetone, ethylacetate, o-dichlorobenzene, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalchol, acetic acid, propionic acid etc, a mixture thereof or the like. The condensation reaction is carried out by using acidic condition: mineral or organic acids, or basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals. The reaction is usually carried out under cooling to refluxing conditions. The final product purified by using chromatographic techniques or by recrystallization.

According to still another embodiment of the present invention, there is provided a process for the preparation of novel pyrimidone derivatives of the

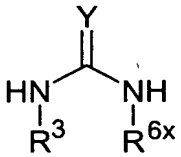
formula (I) where R^2 and R^3 represent unsubstituted or substituted aryl group wherein either R^2 and R^3 are substituted with atleast one of the groups selected from alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl and all other symbols are as defined earlier which comprises

(i) Reacting a compound of the formula (Ia)



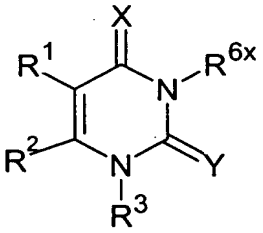
(Ia)

where R' represent (C_1-C_3) alkyl group and all other symbols are as defined earlier, with a compound of the formula (Ie)



(Ie)

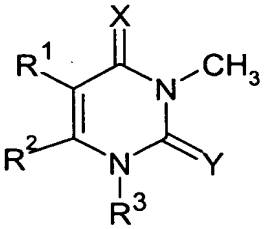
where R^3 and R^{6x} are as defined earlier, to produce a compound of formula (If)



(If)

where all symbols are as defined earlier,

(ii) Converting a compound of formula (If) where R^{6x} represents hydrogen to a compound of formula (Ig)



(Ig)

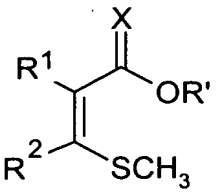
where all symbols are as defined earlier,

The reaction of compound of formula (Ia) with compound of formula (Ie) to produce a compound of formula (If) may be carried out using appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethylacetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalchol, acetic acid, propionic acid etc, a mixture thereof or the like. The condensation reaction is carried out by using acidic condition: mineral or organic acids, or basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals. The reaction is usually carried out under cooling to refluxing conditions. The final product purified by using chromatographic techniques or by recrystallization.

The conversion of compound of formula (If) to a compound of formula (Ig) may be carried out using dimethylsulfate or methyl halide or diazomethane as alkylating agent in aqueous or non-aqueous media using basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals.

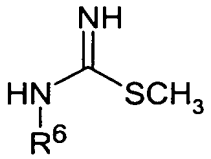
According to still another embodiment of the present invention, there is provided a process for the preparation of novel pyrimidone derivatives of the formula (I) where R^4 represent $-Z-R^7$, Z represents -NH-, R^6 and R^7 represent unsubstituted or substituted aryl group wherein either R^6 and R^7 are substituted with atleast one of the groups selected from alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, sulfamoyl and all other symbols are as defined earlier which comprises

(i) Reacting a compound of the formula (Ia)



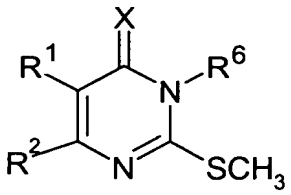
(Ia)

where R' represent (C_1-C_3) alkyl group and R^1, R^2, X are as defined earlier, with a compound of the formula (Ih)



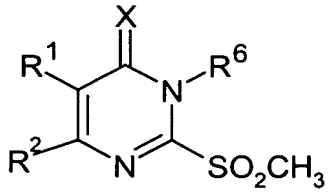
(Ih)

where R^6 is as defined earlier, to produce a compound of formula (Ii),



(Ii)

(ii) Oxidizing the compound of formula (Ii) to produce a compound of formula (Ij)



(Ij)

where all symbols are as defined earlier,

(iii) Reacting a compound of formula (Ij) with a compound of formula (Ik)

R^7 –NH_2 **(Ik)**

where R^7 is as defined earlier to produce a compound of formula (I) defined above.

The reaction of compound of formula (Ia) with a compound of formula (Ih) to produce a compound of formula (Ii) may be carried out using appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethylacetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalchol, acetic acid, propionic acid etc, a mixture thereof or the like. The condensation reaction is carried out by using acidic condition: mineral or organic acids, or basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals. The reaction is usually carried out under cooling to refluxing conditions. The final product purified by using chromatographic techniques or by recrystallization.

Oxidation of compound of formula (Ii) to produce a compound of formula (Ij) may be carried out using conventional oxidising agents such as potassium peroxymonosulfate (Oxone), hydrogen peroxide, tert-butylperoxide, Jones reagent, peracid [e.g peracetic acid, perbenzoic acid, m-chloroperbenzoic acid etc], chromic acid, potassium permanganate, alkali metal periodate [e.g sodium periodate, etc], magnesium mono peroxypthalate, osmium tetroxide/N-methylmorpholine-N-oxide, sodium tungstate, and the like. The oxidation is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [eg. Methanol, ethanol, etc.], a mixture thereof or the like. The reaction is usually carried out under cooling to refluxing conditions.

The reaction of compound of formula (Ij) with a compound of formula (Ik) to produce a compound of formula (I) may be carried out using

appropriate solvents like toluene, xylene, tetrahydrofuran, dioxane, chloroform, dichloromethane, dichloroethane, o-dichlorobenzene, acetone, ethylacetate, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, ethanol, methanol, isopropylalcohol, tert-butylalchol, acetic acid, propionic acid etc, a mixture thereof or the like. The reaction is carried out by using basic conditions viz. carbonates, bicarbonates, hydrides, hydroxides, alkyls and alkoxides of alkali metals and alkaline earth metals. The reaction is usually carried out under cooling to refluxing conditions. The final product purified by using chromatographic techniques or by recrystallization.

According to yet another embodiment of the present invention there is provided a process for the conversion of novel pyrimidone derivatives of the formula (I) wherein any of the groups R^1, R^2, R^3, R^7, R^6 are substituted with alkylthio, arylthio may be converted to novel pyrimidone derivatives of the formula (I) wherein any of the groups R^1, R^2, R^3, R^7, R^6 are substituted with alkylsulfonyl, arylsulfonyl groups by using suitable oxidising reagent. The suitable oxidising may be potassium peroxymonosulfate (Oxone), hydrogen peroxide, tert-butylperoxide, Jones reagent, peracid [e.g peracetic acid, perbenzoic acid, m-chloroperbenzoic acid etc], chromic acid, potassium permanganate, alkali metal periodate [e.g sodium periodate, etc], magnesium mono peroxypthalate, osmium tetroxide/N-methylmorpholine-N-oxide, sodium tungstate, and the like. The oxidation is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [eg. methanol, ethanol, etc.], a mixture thereof or the like. The reaction temperature is usually carried out under cooling to refluxing conditions.

According to yet another embodiment of the present invention there is provided a process for the conversion of novel pyrimidone derivatives of the formula (I) wherein any of the groups R^1, R^2, R^3, R^7, R^6 are substituted with alkylsulfonyl, arylsulfonyl may be converted to novel pyrimidone derivatives of the formula (I) wherein any of the groups R^1, R^2, R^3, R^7, R^6 are substituted

with sulfamoyl group by using the procedure described in the literature (Huang et.al. Tetrahedron Lett. 1994, 39, 7201).

The pharmaceutically acceptable salts are prepared by reacting the compound of formula (I) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, tetrahydrofuran, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases such as diethanolamine, α-phenylethylamine, benzylamine, piperidine, morpholine, pyridine, hydroxyethylpyrrolidine, hydroxyethylpiperidine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Amino acid such as glycine, alanine, cystine, cysteine, lysine, arginine, phenylalanine, guanidine etc may be used for the preparation of amino acid salts. Alternatively, acid addition salts wherever applicable are prepared by the treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, tetrahydrofuran, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine,

cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (I) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (I) may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formula (I) forming part of this invention may be prepared by crystallization of compound of formula (I) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

Pharmaceutically acceptable solvates of the compounds of formula (I) forming part of this invention may be prepared by conventional methods such as dissolving the compounds of formula (I) in solvents such as water, methanol, ethanol, mixture of solvents such as acetone:water, dioxane:water, N,N-dimethylformamide:water and the like, preferably water and recrystallizing by using different crystallization techniques.

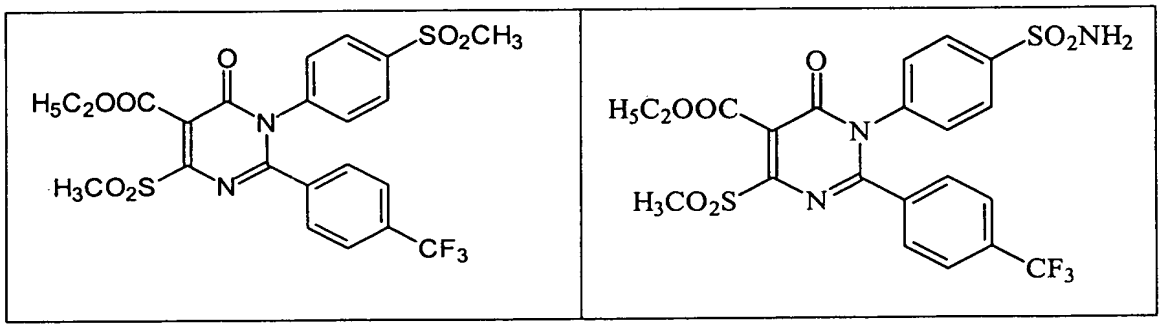
The present invention provides a pharmaceutical composition, containing the compounds of the general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their

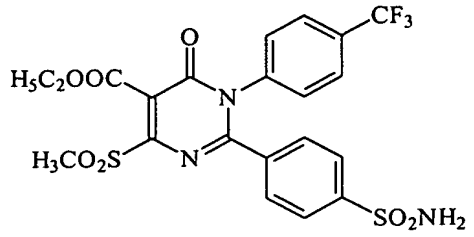
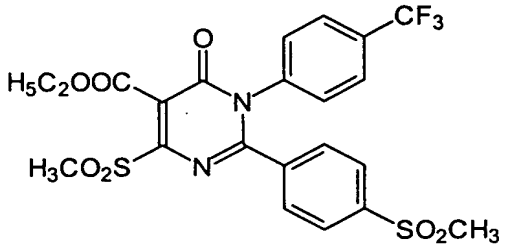
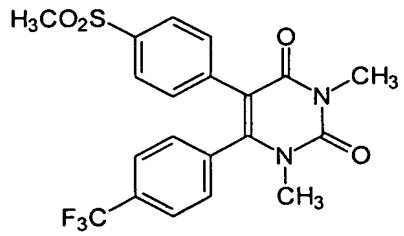
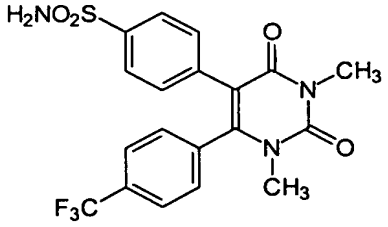
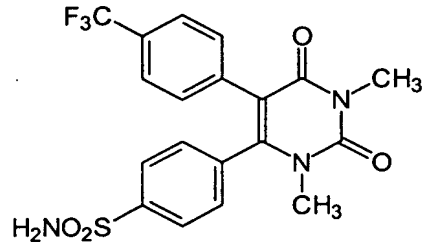
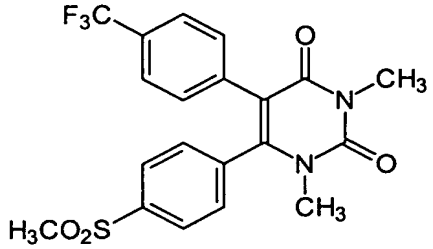
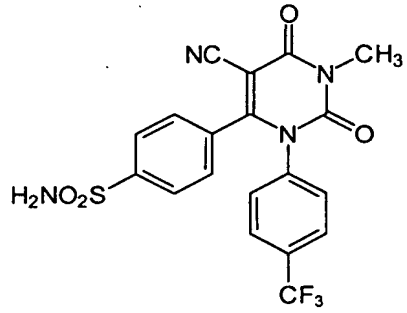
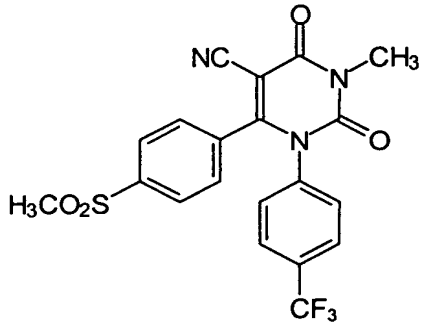
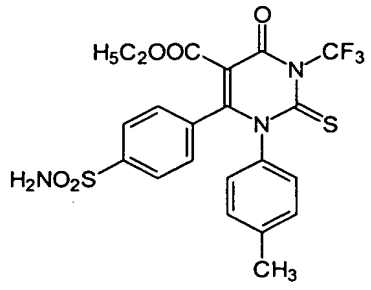
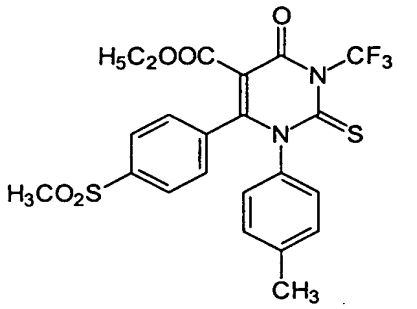
polymorphs, their pharmaceutically acceptable hydrates and solvates in combination with the usual pharmaceutically employed carriers, diluents and the like, useful for the treatment of inflammation, arthritis, pain, fever, psoriasis, allergic diseases, asthma, inflammatory bowel syndrome, gastro-intestinal ulcers, cardiovascular disorders including ischemic heart disease, atherosclerosis, cancer, ischemic-induced cell damage, particularly brain damage caused by stroke, other pathological disorders associated with free radicals.

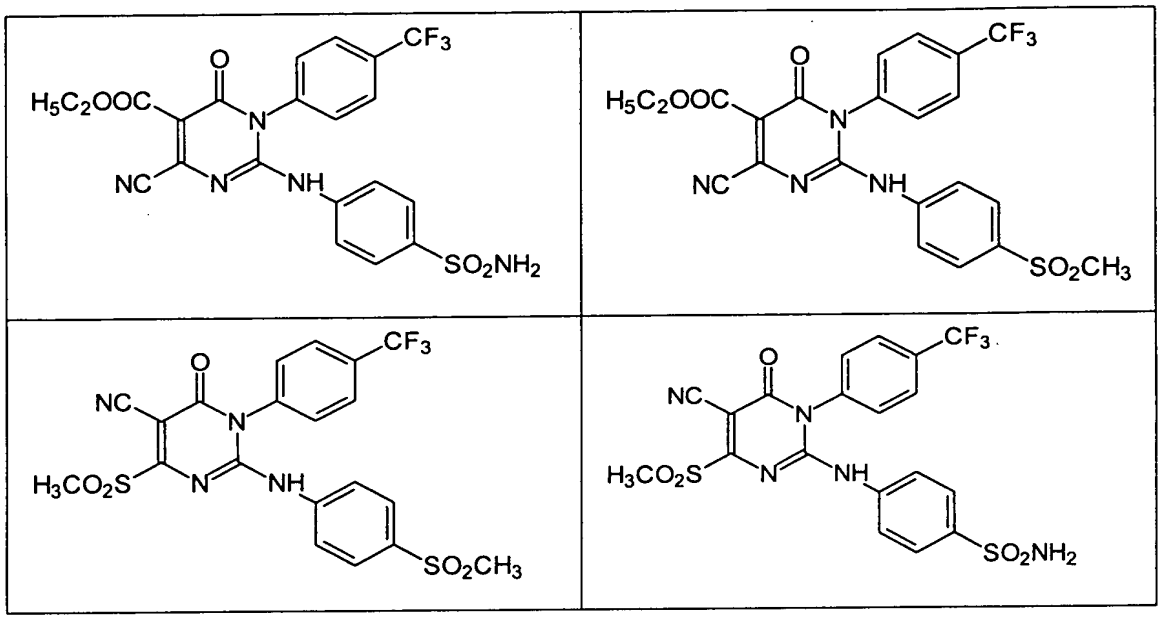
The pharmaceutical composition may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like, may contain flavoring agents, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 20 %, preferably 1 to 10 % by weight of active compound, the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents.

The novel pyrimidone derivatives of the formula (I) will be screened for their *in vitro* COX-2 and COX-1 inhibition activity and *in vivo* anti-inflammatory and analgesic activity by using standard protocols used for the screening.

Structures of few representative examples are as given here under





Dated this tenth (10th) day of April 2002

for Orchid Chemicals & Pharmaceuticals Ltd.,

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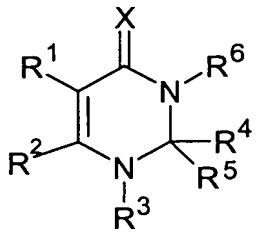
Dr. C. B. Rao

Dy. Managing Director

Abstract

The present invention provides novel pyrimidone derivatives of the general formula (I).



(I)

their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions containing them.

The present invention also provides a process for the preparation of the above said novel pyrimidone derivatives of the formula (I) their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their hydrates, their solvates, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them.